TRI-LUMA - fluocinolone acetonide, hydroquinone and tretinoin cream
Galderma Laboratories, L.P.

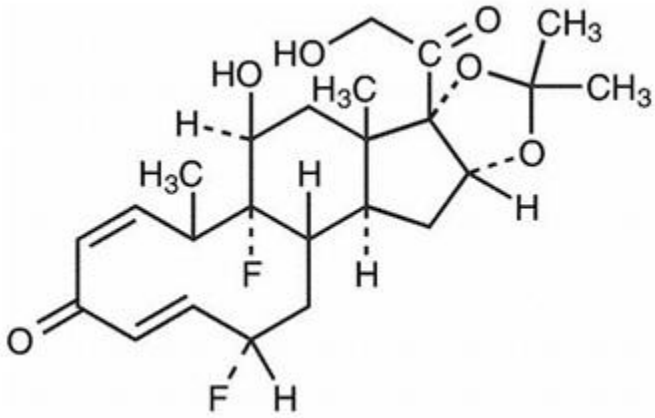
DESCRIPTION

TRI-LUMA® Cream (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) contains fluocinolone acetonide, USP, hydroquinone, USP, and tretinoin, USP, in a hydrophilic cream base for topical application.

Fluocinolone acetonide is a synthetic fluorinated corticosteroid for topical dermatological use and is classified therapeutically as an anti-inflammatory. It is a white crystalline powder that is odorless and stable in light.

The chemical name for fluocinolone acetonide is: (6α,11β,16α)-6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,-4-diene-3,20-dione.

The molecular formula is $C_{24}H_{30}F_2O_6$ and molecular weight is 452.50. Fluocinolone acetonide has the following structural formula:



Hydroquinone is classified therapeutically as a depigmenting agent. It is prepared from the reduction of *p*-benzoquinone with sodium bisulfite. It occurs as fine white needles that darken on exposure to air.

The chemical name for hydroquinone is: 1,4-benzenediol.

The molecular formula is $C_6H_6O_2$ and molecular weight is 110.11.

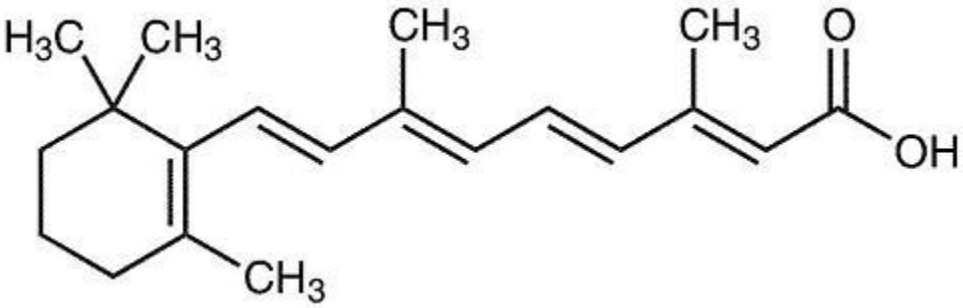
Hydroquinone has the following structural formula:

Tretinoin is all-*trans*-retinoic acid formed from the oxidation of the aldehyde group of retinene to a carboxyl group. It occurs as yellow to light-orange crystals or crystalline powder with a characteristic odor of ensilage. It is highly reactive to light and moisture. Tretinoin is classified therapeutically as a keratolytic.

The chemical name for tretinoin is: (*all-E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid.

The molecular formula is $C_{20}H_{28}O_2$ and molecular weight is 300.44.

Tretinoin has the following structural formula:



Each gram of TRI-LUMA® Cream contains **Active:** fluocinolone acetonide 0.01% (0.1 mg), hydroquinone 4% (40 mg), and tretinoin 0.05% (0.5 mg). **Inactive:** butylated hydroxytoluene, cetyl alcohol, citric acid, glycerin, glyceryl stearate, magnesium aluminum silicate, methyl gluceth-10, methylparaben, PEG-100 stearate, propylparaben, purified water, sodium metabisulfite, stearic acid, and stearyl alcohol.

CLINICAL PHARMACOLOGY

One of the components in TRI-LUMA® Cream, hydroquinone, is a depigmenting agent, and may interrupt one or more steps in the tyrosine-tyrosinase pathway of melanin synthesis. However, the mechanism of action of the active ingredients in TRI-LUMA® Cream in the treatment of melasma is unknown.

Pharmacokinetics: Percutaneous absorption of unchanged tretinoin, hydroquinone and fluocinolone acetonide into the systemic circulation of two groups of healthy volunteers (Total n=59) was found to be minimal following 8 weeks of daily application of 1g (Group I, n=45) or 6g (Group II, n=14) of TRI-LUMA® Cream.

For tretinoin quantifiable plasma concentrations were obtained in 57.78% (26 out of 45) of Group I and 57.14% (8 out of 14) of Group II subjects. The exposure to tretinoin as reflected by the Cmax values ranged from 2.01 to 5.34 ng/mL (Group I) and 2.0 to 4.99 ng/mL (Group II). Thus, daily application of TRI-LUMA® Cream resulted in a minimal increase of normal endogenous levels of tretinoin. The circulating tretinoin levels represent only a portion of total tretinoin-associated retinoids, which would include metabolites of tretinoin and that sequestered into peripheral tissues.

For hydroquinone quantifiable plasma concentrations were obtained in 18% (8 out of 44) Group I subjects. The exposure to hydroquinone as reflected by the Cmax values ranged from 25.55 to 86.52 ng/mL. All Group II subjects (6g dose) had post-dose plasma hydroquinone concentrations below the quantitation limit. For fluocinolone acetonide, Groups I and II subjects had all post-dose plasma concentrations below quantitation limit.

Clinical Studies: Two adequate and well-controlled efficacy and safety studies were conducted in 641 patients between the ages of 21 to 75 years, having skin phototypes I-IV and moderate to severe melasma of the face. TRI-LUMA® Cream was compared with 3 possible combinations of 2 of the 3 active ingredients [(1) hydroquinone 4% (HQ) + tretinoin 0.05% (RA); (2) fluocinolone acetonide 0.01% (FA) + tretinoin 0.05% (RA); (3) fluocinolone acetonide 0.01% (FA) + hydroquinone 4% (HQ)], contained in the same vehicle as TRI-LUMA® Cream. Patients were instructed to apply their study medication each night, after washing their face with a mild soapless cleanser, for 8 weeks. Instructions were given to apply a thin layer of study medication to the hyperpigmented lesion, making sure to cover the entire lesion including the outside borders extending to the normal pigmented skin. Patients were provided a mild moisturizer for use as needed. A sunscreen with SPF 30 was also provided with instructions for daily use. Protective clothing and avoidance of sunlight exposure to the face was recommended.

Patients were evaluated for melasma severity at Baseline and at Weeks 1, 2, 4, and 8 of treatment. Primary efficacy was based on the proportion of patients who had an investigators' assessment of treatment success, defined as the clearing of melasma at the end of the eight-week treatment period. The majority of patients enrolled in the two studies were white (approximately 66%) and female (approximately 98%). TRI-LUMA® Cream was demonstrated to be significantly more effective than any of the other combinations of the active ingredients.

PRIMARY EFFICACY ANALYSIS:

Investigators' Assessment of Treatment Success* At the End of 8 Weeks of Treatment

		TRI-LIMA®	HQ+RA	FA+RA	FA+HQ
Study No. 1	Number of Patients	85	83	85	85
	No. of Successes	32	12	0	3
	Proportion of Successes	38%	15%	0	4%
	p-value		<0.001	<0.001	<0.001
Study No. 2	Number of Patients	76	75	76	76
	No. of Successes	10	3	3	1
	Proportion of Successes	13%	4%	4%	1%
	p-value		0.045	0.042	0.005

*Treatment success was defined as melasma severity score of zero (melasma lesions cleared of hyperpigmentation).

p-value is from Cochran-Mantel-Haenszel chi-square statistics controlling for pooled investigator and comparing TRI-LUMA® Cream to the other treatment groups.

In the Investigators' assessment of melasma severity at Day 56 of treatment, the following table shows the clinical improvement profile for all patients treated with TRI-LUMA® Cream based on severity of their melasma at the start of treatment.

Investigators' Assessment of Change iin Melasma Severity from Baseline to Day 56 of Treatment (combined results from studies 1 and 2)

	Baseline		Number (%) of Patients at Day 56[a]				
			Cleared[b]	Mild[b]	Moderate[b]	Severe[b]	Missing[b]
	Severity Rating	N	N (%)	N (%)	N (%)	N (%)	N (%)
TRI-LUMA®	Moderate	124	36 (29)	63 (51)	18 (15)	0 (0)	7 (6%)

Cream N=161	Severe	37	6 (16)	19 (51)	9 (24)	2 (5)	1 (3%)

[a] Assessment based on patients with severity scores at Day 56. Percentages are based on the total number in the treatment group population.

[b] Does not include patients who cleared before Day 56 or were missing from the Day 56 assessment.

Assessment Scale: Cleared (melasma lesions approximately equivalent to surrounding normal skin or with minimal residual hyperpigmentation); Mild (slightly darker than the surrounding normal skin); Moderate (moderately darker than the surrounding normal skin); Severe (markedly darker than the surrounding normal skin).
Patients experienced improvement of their melasma with the use of TRI-LUMA® Cream as early as 4 weeks. Among the 7 patients that cleared at the end of 4 weeks of treatment with TRI-LUMA® Cream at which time treatment was stopped, 3 patients maintained remission while 4 patients had relapse at the final 8th week evaluation point.
After 8 weeks of treatment with the study drug, patients entered into an open-label long-term safety study in which TRI-LUMA® CREAM was given on an as-needed basis for the treatment of melasma. The objective was to provide evidence of local and systemic safety with cumulative use of TRI-LUMA® Cream for longer than 6 months, up to one year. Patients were instructed to apply TRI-LUMA® Cream once daily at nighttime after washing their face with a mild soapless cleanser, also provided a mild moisturizer for use as needed and a sunscreen with SPF 30 for daily use, in combination with the use of protective clothing and avoidance of sunlight exposure to the face. Patients were treated daily until melasma is resolved, and then retreated when melasma recurred. The majority of patients used TRI-LUMA® for no more than two courses of treatment and these patients experienced longer remissions. Both the duration of treatment and interval of time between treatment courses decreased with increasing number of treatment courses. Additionally, 24 patients (approximately 8%) cleared of melasma without re-occurrence, for a period of one year.

INDICATIONS AND USAGE
TRI-LUMA® Cream is indicated for the short-term intermittent treatment of moderate to severe melasma of the face, in the presence of measures for sun avoidance, including the use of sunscreens.
The following are important statements relating to the indication and usage of TRI-LUMA® Cream:
- TRI-LUMA® Cream, a combination drug product containing corticosteroid, retinoid, and bleaching agent, was proven safe for the intermit-tent treatment of melasma, with cumulative treatment time of at least 180 days. Because melasma usually recurs upon discontinuation of TRI-LUMA® Cream, patients can be re-treated with TRI-LUMA® until melasma is resolved. Patients need to avoid sunlight exposure, use sunscreen with appropriate SPF, wear protective clothing, and change to non-hormonal forms of birth control, if hormonal methods are used.

- In clinical trials used to support the use of TRI-LUMA® Cream in the treatment of melasma, patients were instructed to avoid sunlight exposure to the face, wear protective clothing and use a sunscreen with SPF 30 each day. They were to apply the study medication each night, after washing their face with a mild soapless cleanser.

- The safety and efficacy of TRI-LUMA® Cream in patients of skin types V and VI have not been studied. Excessive bleaching resulting in undesirable cosmetic effect in patients with darker skin cannot be excluded.

- The safety and efficacy of TRI-LUMA® Cream in the treatment of hyperpigmentation conditions other than melasma of the face have not been studied.

- Because pregnant and lactating women were excluded from, and women of child-bearing potential had to use birth control measures in the clinical trials, the safety and efficacy of TRI-LUMA® Cream in pregnant women and nursing mothers have not been established (See PRECAUTIONS, Pregnancy).

CONTRAINDICATIONS
TRI-LUMA® Cream is contraindicated in individuals with a history of hypersensitivity, allergy, or intolerance to this product or any of its components.

WARNINGS
TRI-LUMA® Cream contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening asthmatic episodes in susceptible people.
The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.
TRI-LUMA® Cream contains hydroquinone, which may produce exogenous ochronosis, a gradual blue-black darkening of the skin, whose occurrence should prompt discontinuation of therapy. The majority of patients developing this condition are Black, but it may also occur in Caucasians and Hispanics.
Cutaneous hypersensitivity to the active ingredients of TRI-LUMA® Cream has been reported in the literature. In a patch test study to determine sensitization potential in 221 healthy volunteers, three volunteers developed sensitivity reactions to TRI-LUMA® Cream or its components.

PRECAUTIONS

General

TRI-LUMA® Cream contains hydroquinone and tretinoin that may cause mild to moderate irritation. Local irritation, such as skin reddening, peeling, mild burning sensation, dryness, and pruritus may be expected at the site of application. Transient skin reddening or mild burning sensation does not preclude treatment. If a reaction suggests hypersensitivity or chemical irritation, the use of the medication should be discontinued.

TRI-LUMA® Cream also contains the corticosteroid fluocinolone acetonide. Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced by systemic absorption of topical corticosteroid while on treatment. If HPA axis suppression is noted, the use of TRI-LUMA® Cream should be discontinued. Recovery of HPA axis function generally occurs upon discontinuation of topical corticosteroids.

Information for Patients

Exposure to sunlight, sunlamp, or ultraviolet light should be avoided. Patients who are consistently exposed to sunlight or skin irritants either through their work environment or habits should exercise particular caution. Sunscreen and protective covering (such as the use of a hat) over the treated areas should be used. Sunscreen use is an essential aspect of melasma therapy, as even minimal sunlight sustains melanocytic activity.

Weather extremes, such as heat or cold, may be irritating to patients treated with TRI-LUMA® Cream. Because of the drying effect of this medication, a moisturizer may be applied to the face in the morning after washing.

Application of TRI-LUMA® Cream should be kept away from the eyes, nose, or angles of the mouth, because the mucosa is much more sensitive than the skin to the irritant effect. If local irritation persists or becomes severe, application of the medication should be discontinued, and the health care provider consulted. Allergic contact dermatitis, blistering, crusting, and severe burning or swelling of the skin and irritation of the mucous membranes of the eyes, nose, and mouth require medical attention.

If the medication is applied excessively, marked redness, peeling, or discomfort may occur.

This medication is to be used as directed by the health care provider and should not be used for any disorder other than that for which it is prescribed.

Laboratory Tests

The following tests may be helpful in evaluating patients for HPA axis suppression:

ACTH or cosyntropin stimulation test

A.M. plasma cortisol test

Urinary free cortisol test

Drug Interactions

Patients should avoid medicated or abrasive soaps and cleansers, soaps and cosmetics with drying effects, products with high concentration of alcohol and astringent, and other irritants or keratolytic drugs while on TRI-LUMA® Cream treatment. Patients are cautioned on concomitant use of medications that are known to be photosensitizing.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to determine the carcinogenic potential of TRI-LUMA® Cream have not been conducted.

Studies of hydroquinone in animals have demonstrated some evidence of carcinogenicity. The carcinogenic potential of hydroquinone in humans is unknown.

Studies in hairless albino mice suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect has been confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

Mutagenicity studies were not conducted with this combination of active ingredients. Published studies have demonstrated that hydroquinone is a mutagen and a clastogen. Treatment with hydroquinone has resulted in positive findings for genetic toxicity in the Ames assay in bacterial strains sensitive to oxidizing mutagens, in *in vitro* studies in mammalian cells, and in the *in vivo* mouse micronucleus assay. Tretinoin has been shown to be negative for mutagenesis in the Ames assay. Additional information regarding the genetic toxicity potential of tretinoin and of fluocinolone acetonide is not available.

A dermal reproductive fertility study was conducted in SD rats using a 10-fold dilution of the clinical formulation. No effect was seen on the traditional parameters used to assess fertility, although prolongation of estrus was observed in some females, and there was a trend towards an increase in pre-and post-implantation loss that was not statistically significant. No adequate study of fertility and early embryonic toxicity of the full-strength drug product has been performed. In a six-month study in minipigs, small testes and severe hypospermia were found when males were treated topically with the full strength drug product.

Pregnancy

Teratogenic Effects
Pregnancy Category C: TRI-LUMA® Cream contains the teratogen, tretinoin, which may cause embryo-fetal death, altered fetal growth, congenital malformations, and potential neurologic deficits. It is difficult to interpret the animal studies on teratogenicity with TRI-LUMA® Cream, because the availability of the dermal applications in these studies cannot be assured, and comparison with clinical dosing is not possible. There are no adequate and well-controlled studies in pregnant women. TRI-LUMA® Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Summary Statement on Teratogenic Risk

TRI-LUMA® Cream contains the teratogen, tretinoin, which may cause embryo-fetal death, altered fetal growth, congenital malformations, and potential neurologic deficits. However, human data have not confirmed an increased risk of these developmental abnormalities when tretinoin is administered by the topical route.

Clinical considerations relevant to actual or potential inadvertent exposure during pregnancy:

In clinical trials involving TRI-LUMA® Cream in the treatment of facial melasma, women of child-bearing potential initiated treatment only after having had a negative pregnancy test and used effective birth control measures during therapy. Thus, safety and efficacy of TRI-LUMA® Cream in pregnancy has not been established. In general, use of drugs should be reduced to a minimum in pregnancy. If a patient has been inadvertently exposed to TRI-LUMA® Cream in pregnancy, she should be counseled on the risk of teratogenesis due to this exposure. The risk of teratogenesis due to topical exposure to TRI-LUMA® Cream may be considered low. However, exposure during the period of organogenesis in the first trimester is theoretically more likely to produce adverse outcome than in later pregnancy.

The prescriber should have the following clinical considerations in making prescribing decisions:

- The potential developmental effects of tretinoin are serious but the risk from topical administration is small.
- Exposure during the period for organogenesis in the first trimester is theoretically more likely to produce adverse outcome than in later pregnancy.
- The risk to the mother for not treating melasma should be determined by the physician with the patient. Mild forms of melasma may not necessarily require drug treatment. TRI-LUMA® Cream is indicated for the treatment of moderate to severe melasma. Melasma may also be managed with other forms of therapy such as topical hydroquinone in the presence of sunlight avoidance, or stopping the use of hormonal birth control methods. If possible, delaying treatment with TRI-LUMA® Cream until after delivery should be considered.
- There are no adequate and well-controlled studies in pregnant women. TRI-LUMA® Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Data Discussion: Tretinoin is considered to be highly teratogenic upon systemic administration. Animal reproductive studies are not available with topical hydroquinone. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

1. Human Data.

- In clinical trials involving TRI-LUMA® Cream in the treatment of facial melasma, women of child-bearing potential initiated treatment only after having had a negative pregnancy test, and used effective birth control measures during therapy. However, 15 women became pregnant during treatment with TRI-LUMA® Cream. Of these pregnancies, 6 resulted in healthy babies, 6 outcomes still unknown, 2 were reported as miscarriages, and 1 case was lost to follow-up.
- Epidemiologic studies have not confirmed an increase in birth defects associated with the use of topical tretinoin. However, there may be limitations to the sensitivity of epidemiologic studies in the detection of certain forms of fetal injury, such as subtle neurologic or intelligence deficits.

2. Animal Data.

- In a dermal application study using TRI-LUMA® Cream in pregnant rabbits, there was an increase in the number of *in utero* deaths and a decrease in fetal weights in litters from dams treated topically with the drug product.

- In a dermal application study in pregnant rats treated with TRI-LUMA® Cream during organogenesis there was evidence of teratogenicity of the type expected with tretinoin. These morphological alterations included cleft palate, protruding tongue, open eyes, umbilical hernia, and retinal folding or dysplasia.

- In a dermal application study on the gestational and postnatal effects of a 10-fold dilution of TRI-LUMA® Cream in rats, an increase in the number of stillborn pups, lower pup body weights, and delay in preputial separation were observed. An increase in overall activity was seen in some treated litters at postnatal day 22 and in all treated litters at five weeks, a pattern consistent with effects previously noted in animals exposed *in utero* with retinoic acids. No adequate study of the late gestational and postnatal effects of the full-strength TRI-LUMA® Cream has been performed.

- It is difficult to interpret these animal studies on teratogenicity with TRI-LUMA® Cream, because the availability of the dermal applications in these studies could not be assured, and comparison with clinical dosing is not possible.

All pregnancies have a risk of birth defect, loss, or other adverse event regardless of drug exposure. Typically, estimates of increased fetal risk from drug exposure rely heavily on animal data. However, animal studies do not always predict effects in humans. Even if human data are available, such data may not be sufficient to determine whether there is an increased risk to the fetus. Drug effects on behavior, cognitive function, and fertility in the offspring are particularly difficult to assess.

Nursing Mothers
Corticosteroids, when systemically administered, appear in human milk. It is not known whether topical application of TRI-LUMA® Cream could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide, hydroquinone, or tretinoin in human milk. Because many drugs are secreted in human milk, caution should be exercised when TRI-LUMA® Cream is administered to a nursing woman. Care should be taken to avoid contact between the infant being nursed and TRI-LUMA® Cream.

Pediatric Use
Safety and effectiveness of TRI-LUMA® Cream in pediatric patients have not been established.

Geriatric Use
Clinical studies of TRI-LUMA® Cream did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
In the controlled clinical trials, adverse events were monitored in the 161 patients who used TRI-LUMA® Cream once daily during an 8-week treatment period. There were 102 (63%) patients who experienced at least one treatment-related adverse event during these studies. In the long-term clinical study, from a total of 314 patients treated with TRI-LUMA® Cream for at least 180 cumulative days, there were 202 (64%) patients who experienced at least one treatment-related adverse event. No significant increase in severity or incidence of the adverse events was observed from long term use of TRI-LUMA® Cream compared with events reported during the 8-week controlled clinical studies. The most frequently reported adverse events that were observed from the controlled clinical trials and the long term safety were erythema, desquamation, and burning, at the site of application. The number and percentages of these events were markedly lower in the long-term study than in the controlled clinical studies. The great majority of these events were mild to moderate in severity.
Adverse events reported by at least 1% of patients and judged by the investigators to be reasonably related to treatment with TRI-LUMA® Cream from the controlled clinical studies and the long-term study are summarized (in decreasing order of frequency).
Incidence and Frequency of Treatment-related Adverse Events with TRI-LUMA®

Cream in at least 1% or more of Patients (N=161)	
Adverse Event	**Number (%) of Patients**
Erythema	66 (41%)
Desquamation	61 (38%)
Burning	29 (18%)
Dryness	23 (14%)
Pruritus	18 (11%)
Acne	8 (5%)
Paresthesia	5 (3%)
Telangiectasia	5 (3%)
Hyperesthesia	3 (2%)
Pigmentary changes	3 (2%)

Irritation	3 (2%)
Papules	2 (1%)
Acne-like rash	1 (1%)
Rosacea	1 (1%)
Dry mouth	1 (1%)
Rash	1 (1%)
Vesicles	1 (1%)

Inan open-label long-term safety study, patients who have had cumulative treatment of melasma with TRI-LUMA® Cream for 6 months showed a similar pattern of adverse events as in the 8-week studies.

Summary of Most Common Treatment-Related Adverse Events (TRAE)[a] Study 29

	Number (%) of Patients	
	Treatment Group	
	TRI-LUMA®	
Preferred Term	**All Patients (N=569)**	**Patients with at least 180 Cumulative Days of TRI-LUMA® Treatment Days (N=314)**
Total number of TRAE[a]	326 (57.29)	202 (64.33)
Application site erythema	166 (29.17)	105 (33.44)
Application site desquamation	145 (25.48)	91 (28.98)
Application site dryness	46 (8.08)	27 (8.60)
Application site burning	38 (6.68)	25 (7.96)
Application site inflammation	31 (5.45)	24 (7.64)
Application site reaction nos	31 (5.45)	17 (5.41)
Application site rash	30 (5.27)	18 (5.73)
Application site pruritus	24 (4.22)	18 (5.73)
Application site pigmentation changes	23 (4.04)	18 (5.73)

[a] Defined as “probably” or “possibly” related to study medication

Data source: Section 14.3, Tables 8.1.1, 8.1.2, and 8.1.3

The severity, incidence and type of adverse events experienced from 6 months cumulative use were not significantly different from the events reported for all patients.

The incidence of application site pigmentation changes that occurred in both the controlled and long-term safety studies included 11 occurrences of hypopigmentation and 18 occurrences of hyperpigmentation in 27 patients.

The following local adverse reactions have been reported infrequently with topical corticosteroids. They may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria.

TRI-LUMA® Cream contains hydroquinone, which may produce exogenous ochronosis, a gradual blue-black darkening of the skin, whose occurrence should prompt discontinuation of therapy.

Cutaneous hypersensitivity to the active ingredients of TRI-LUMA® Cream has been reported in the literature. In a patch test study to determine sensitization potential in 221 healthy volunteers, three volunteers developed sensitivity reactions to TRI-LUMA® Cream or its components.

DOSAGE AND ADMINISTRATION

TRI-LUMA® Cream should be applied once daily at night. It should be applied at least 30 minutes before bedtime.

Gently wash the face and neck with a mild cleanser. Rinse and pat the skin dry. Apply a thin film of the cream to the hyperpigmented areas of melasma including about 1/2 inch of normal appearing skin surrounding each lesion. Rub lightly and uniformly into the skin. Do not use occlusive dressing.

During the day, use a sunscreen of SPF 30, and wear protective clothing. Avoid sunlight exposure. Patients may use moisturizers and/or cosmetics during the day.

Therapeutic effects may be observed as early as 4 weeks. Use TRI-LUMA® Cream daily for as long as the melasma lesions persist. Treatment should be discontinued when melasma is resolved. When melasma recurs, retreat with TRI-LUMA® Cream until the condition clears.

HOW SUPPLIED

TRI-LUMA® Cream is supplied in 30 g aluminum tubes, **NDC** 0299-5950-30.

Storage: Keep tightly closed. Store at controlled room temperature 68° to 77°F (20°-25°C).

Protect from freezing.

Marketed by:

GALDERMA LABORATORIES, L.P., Fort Worth, TX 76177 USA

GALDERMA is a registered trademark.

www.triluma.com

Manufactured by:

Hill Laboratories, Inc., Sanford, FL 32773 USA

20024-1203 Revised: December 2003

PATIENT INFORMATION

For External Use Only.

Not for Ophthalmic Use.

TRI-LUMA®Cream

(fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%)

Read this information carefully before you begin treatment. Read the information you get whenever you get more medicine. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about TRI-LUMA® (try-LOOM-ah), ask your doctor. Only your doctor can determine if TRI-LUMA® is right for you.

What is the most important information I should know about TRI-LUMA® Cream?

Use of TRI-LUMA® Cream in pregnant women may carry the chance of having birth defects in the baby. Tell your doctor if you are pregnant, may be pregnant, or plan to become pregnant. Your doctor will talk with you about the benefits and risks of using TRI-LUMA® during pregnancy to help decide if the benefits for you are greater than the risks. You may decide to delay treatment until after your baby is born.

If you become pregnant while taking TRI-LUMA® Cream, tell your doctor right away. You should discuss the chances that your baby may be harmed. Using TRI-LUMA® Cream early in pregnancy may be more likely to produce birth defects than using it later in pregnancy.

What is TRI-LUMA® Cream?

TRI-LUMA® (try-LOOM-ah) Cream is a medicine with three active components. You put TRI-LUMA® Cream on your face to treat a skin condition called melasma. Melasma consists of dark (hyperpigmented) spots on facial skin, especially on the cheeks and forehead. This condition usually happens with hormone changes.

TRI-LUMA® Cream is for short-term and intermittent long-term treatment of **moderate to severe** melasma of the face, in the presence of measures for sun avoidance, including the use of sunscreens.

TRI-LUMA® Cream showed a significantly favorable safety profile for the long-term treatment of melasma, up to 6 months. Milder forms of melasma may not need treatment with medicine. Melasma can also be managed by staying out of the sun or by stopping the use of birth control methods that involve hormones.

In clinical studies, after 8 weeks of treatment with TRI-LUMA® Cream, most patients had improvements, with 42 (26%) out of 161 patients experiencing complete clearing of their melasma. In most patients treated with TRI-LUMA® Cream, melasma came back after treatment was stopped. If the underlying causes of melasma, such as the use of certain birth control pills or too much exposure to sunlight, are not removed, melasma will come back when you stop treatment. In the long-term studies, patients were treated with TRI-LUMA® Cream on and off, whenever their melasma comes back until it clears. About 300 patients used TRI-LUMA® Cream intermittently (not continuously) for 180 days, and majority of the side effects were mild in severity. **TRI-LUMA® Cream may improve your melasma, but it is NOT a cure.**

Who should not use TRI-LUMA® Cream?

Do not use TRI-LUMA® if you are allergic to the medicine or any of its ingredients. See the end of this leaflet for a list of ingredients.

What should I tell my doctor before taking TRI-LUMA®?

If you are pregnant, think you are pregnant, plan to be pregnant or are nursing an infant, tell your doctor. Your doctor will decide with you whether the benefits in using TRI-LUMA® Cream will be greater than the risks. If possible, delay treatment with TRI-LUMA® Cream until after the baby is born.

Tell your doctor about all the other medicines and skin products you use, including prescription and non-prescription medicines, cosmetics, and supplements. They may make your skin more sensitive to sunlight.

How should I use TRI-LUMA® Cream?

TRI-LUMA® Cream should be used as instructed by your doctor.

To help you use the medicine correctly, follow these steps:

- Gently wash your face with a mild cleanser. Don’t use a wash cloth to apply the cleanser, just your fingers. Rinse and pat your skin dry.

- Apply TRI-LUMA® Cream at night, at least 30 minutes before bedtime.

- Put a small amount (pea sized or 1/2 inch or less) of TRI-LUMA® Cream on your fingertip.
  Apply a thin coat onto the discolored spot(s). Include about 1/2 inch of normal skin surrounding the affected area. After you have used the medicine for a while, you may find that you need slightly less to do the job.

- Rub the medicine lightly and uniformly into your skin. The medicine should become invisible almost at once. If you can still see it, you are using too much.

- Keep the medicine away from the corners of your nose, your mouth, eyes and open wounds.
  Spread it away from those areas when applying it.

- **Do not** use more TRI-LUMA® Cream or apply it more often than recommended by your doctor.
  Too much TRI-LUMA® Cream may irritate your skin, waste medicine, and won't give you faster or better results.

- Do not cover the treated area with anything after applying TRI-LUMA® Cream.

- If your skin gets too irritated, stop using TRI-LUMA Cream, and let your doctor know.

- To help avoid skin dryness, you may use a moisturizer in the morning after you wash your face.

- You may also use a moisturizer and cosmetics during the day.

Use a sunscreen of at least SPF 30 and a wide-brimmed hat over the treated areas. It requires only a small amount of sunlight to worsen melasma. Melasma can get worse even if you don't get sunburn.
Only your doctor knows which other medicines may be helpful during treatment, and will tell you about them if needed. Do not use other medicines unless your doctor approves them.
If you get sunburned, stop using TRI-LUMA® Cream until your skin is healed.
After stopping TRI-LUMA® treatment, continue to protect your skin from sunlight.

What should I avoid while using TRI-LUMA® Cream?

Sunlight or ultraviolet light. Too much natural sunlight or artificial sunlight from a sunlamp can cause sunburn. Dark skin patches may become darker when the skin is exposed to sunlight. You don't have to have a sunburn to make your melasma worse.
TRI-LUMA® can make your skin more likely to get sunburn or develop other unwanted effects from the sun. Protect your skin from natural sunlight as much as possible to help prevent further darkening of existing dark patches and formation of new ones. Staying out of the sun is especially important for women who take birth control pills or hormone replacement therapy, and for people who have had dark patches in the past.
Use an effective sunscreen **any time you are outside**, even on hazy days. The sunscreen should have SPF (sun protection factor) of 30 or more. Use sunscreen year-round on areas of the skin that are regularly exposed to sunlight, such as your face and hands. If possible, protect the treated area from sunlight exposure.
If you spend a lot of time outside, be especially careful of sunlight. Ask your doctor what SPF level will give you the needed high level of protection. If you will be outside, wear protective clothing, including a hat.
Do not use sunlamps while you use TRI-LUMA® Cream.
Heat, wind and cold. Heat and cold tend to dry or irritate normal skin. Skin treated with TRI-LUMA® Cream may be more likely to react to heat and cold. Your doctor can recommend ways to manage your melasma under these conditions.
Other skin products and medicines. Avoid products that may dry or irritate your skin. These may include soaps and cleansers that are rough or cause drying; certain astringents, such as alcohol-containing products, soaps and toiletries containing alcohol, spices, or lime; or certain medicated soaps, shampoos, and hair permanent products. Do not use any other medicines with TRI-LUMA® Cream unless you have consulted your doctor. The medicines and product you have used in the past may cause redness or peeling when used with TRI-LUMA®.

What are the possible side effects of TRI-LUMA® Cream?

A very few patients may get severe allergic reactions from TRI-LUMA®. This includes people allergic to sulfites. **They may have trouble breathing or severe asthma attacks, which can be life-threatening.**
While you use TRI-LUMA® Cream, your skin may develop mild to moderate redness, peeling, burning, dryness, or itching.
TRI-LUMA® Cream contains a corticosteroid medicine as one of its active components. The following side effects have been reported with application of corticosteroid medicines to the skin: itching, irritation, dryness, infection of the hair follicles, acne, change in skin color, inflammation around the mouth, allergic skin reaction, skin infection, skin thinning, stretch marks, and sweat problems.

Stop using TRI-LUMA® Cream and contact your doctor if you have

- severe or continued irritation, blistering, oozing, scaling, or crusting

- severe burning or swelling of your skin

- irritation of your eyes, nose, and mouth

Some patients using TRI-LUMA® Cream develop dark spots on their skin (hyperpigmentation), tingling, increased skin sensitivity, rash, acne, skin redness caused by a condition called rosacea, skin bumps, blisters, or tiny red lines or blood vessels showing through the skin (telangiectasia).

If you are concerned about how your skin is reacting to the medicine, call your doctor.

General information about prescription medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use TRI-LUMA® for a condition for which it was not prescribed. Do not give TRI-LUMA® to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about TRI-LUMA®. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about TRI-LUMA ® that is written for health professionals.

Ingredients: TRI-LUMA® Cream contains fluocinolone acetonide, hydroquinone, and tretinoin as active ingredients, as well as the following in the cream base: butylated hydroxytoluene, cetyl alcohol, citric acid, glycerin, glyceryl stearate, magnesium aluminum silicate, methyl gluceth-10, methylparaben, PEG-100 stearate, propylparaben, purified water, sodium metabisulfite, stearic acid and stearyl alcohol.

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